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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/023,317	12/17/2001	Christian Plank	VOS-22	2272

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EXAMINER	
ANGELL, JON E	
ART UNIT	**PAPER NUMBER**
1635	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/22/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/023,317	PLANK ET AL.	
	Examiner	Art Unit	
	Jon Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,13,14 and 16-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,13,14 and 16-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/27/2006 has been entered.

Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Claims 1-11, 13, 14, 16-18 are currently pending and are examined herein.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11, 13, 14, 16-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

In this case, the claims are drawn to a composition comprising a carrier and a complex wherein the complex comprises a nucleic acid molecule and a charged copolymer wherein the charged copolymer is bound in the complex via ionic interactions and has the general formula as defined by formula I in claim 1. It is noted that the general formula as defined in claim 1 encompasses an enormous amount of different copolymer structures. The only disclosed use of composition is for delivery of nucleic acid molecules into cells wherein the nucleic acid molecules have a biological affect when delivered into the cells. Therefore, the function of the composition is for delivery of nucleic acid molecules into cells. The genus of compositions encompassed by the claims is enormous because each composition could include a vast number of different copolymers and carriers wherein the structure of each carrier and of each copolymer differs. Since each composition encompassed by the claims is composed of a different combination of copolymer and carrier, each composition differs in its ability to facilitate delivery of a nucleic acid molecule into a cell and the claims may encompass compositions which do not facilitate delivery of nucleic acid molecules into cells. The specification has disclosed PEI/nucleic acid-P3YE5C (Example 9), Polylysine/nucleic acid-P3INF7 (Example 10), DOTAPcholesterol/nucleic acid-P3YE5C (Example 11), DOTAP/cholesterol/nucleic acid-P6YE5C (Example 12), and PEI/nucleic acid-P6YE5C (Example 12), which were shown in the

indicated Examples as capable of delivering the nucleic acid molecule into a cell. However, the specification does not sufficiently describe the genus of compositions encompassed by the claims such that it would be readily apparent to one of skill in the art which compositions had the desired function (the ability to deliver the nucleic acid molecule into a cell) and which ones couldn't without performing additional experimentation. Accordingly, in the absence a sufficient disclosure, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states, "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the compositions having the intended function other than the ones specifically indicated above; therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

Therefore, only the compositions comprising PEI/nucleic acid-P3YE5C (Example 9), Polylysine/nucleic acid-P3INF7 (Example 10), DOTAP/cholesterol/nucleic acid-P3YE5C

(Example 11), DOTAP/cholesterol/nucleic acid-P6YE5C (Example 12), and PEI/nucleic acid-P6YE5C (Example 12) meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).)

Claims 1-11, 13, 14, 16-18 are also rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions comprising PEI/nucleic acid-P3YE5C (Example 9), Polylysine/nucleic acid-P3INF7 (Example 10), DOTAPcholesterol/nucleic acid-P3YE5C (Example 11), DOTAP/cholesterol/nucleic acid-P6YE5C (Example 12), and PEI/nucleic acid-P6YE5C (Example 12) and methods of using these composition and a method of transferring a nucleic acid into a cell using one of these specific compositions, does not reasonably provide enablement for the entire scope encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

> *Wands* states on page 1404,
> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The claims are drawn to a composition that is useful for transfer of nucleic acid molecules into cells wherein the composition comprises a complex comprising a nucleic acid molecule and a charged copolymer wherein the charge copolymer is bound in the complex via ionic interactions. The claims encompass a vast number of different compositions considering every possible copolymer encompassed by Formula I as defined in claim 1.

The relevant art teaches that there are a number of obstacles which must be overcome when using polymers for delivering nucleic acid molecules into cells. Specifically, Finsinger et al. (Gene Therapy, 2000; Vol. 7, pages 1183-1192) teaches,

> "In particular, it has been shown that nonviral gene vectors or their constituents interact strongly with blood components such as the complement system and other blood proteins. Such opsonization of alters the physico-chemical characteristics of vectors, may interfere with vector targeting, and is of concern if vectors are to be applied in humans. Consequently, one major objective in nonviral vector development is to devise vectors which are inert in the in vivo environment during the delivery phase. Gene delivery in vivo comprises an extracellular and intracellular delivery problem where solutions in one part must be compatible with the requirements of the other... In lipsome and nanoparticle technology, poly(ethylene glycol) has been used to confer to these drug carriers the desired stability during the extracellular delivery phase. For the same purpose, PEG has been grafted covalently to preassembled polycation-DNA complexes. It was the aim of the work presented here to develop a new class of protective copolymers (PROCOPs) based on PEG which are assembled with nonviral gene vectors by electrostatic interaction." (See page 1183); and,

> "Surface charge, particle size, and colloidal stability are interdependent physical characteristics of nonviral gene vectors with a strong impact on their biological properties including their efficiencies of gene delivery. The excess positive charge of lipoplexes and polyplexes, which is required for full DNA compaction and nuclease resistance, implies strong interactions with solutes (eg blood proteins, erythrocytes) and the extracellular matrix under in vivo conditions. The mostly undesired consequences can be

> unintentional vector targeting, complement activation, vector inactivation, and clearance by the reticulo-endothelial system." (See paragraph bridiging pages 1186-1187).

Additionally, Choi et al (WO 9929839) teaches,

> "On the other hand, non-viral gene delivery systems, such as cationic liposomes... have their drawbacks. Even though they seem to be safe for human clinical use, typical non-viral systems provide low transfection efficiencies, or cause precipitation of the nucleic acids... At present, LIPOFECTIN... protocol seems to be the most reliable in this category... but it bears the disadvantage of high toxicity..." (See page 2).

Choi et al. teach the design and use of a polymeric gene carrier comprising a grafted copolymer having a straight chain amphiphillic side polymers grafted to a polycationic main polymer (e.g., see abstract).

Therefore, although co-polymers were known in the art as being useful for gene delivery, there were still a number of obstacles that need to be overcome. Furthermore, the art only appears to teach the use of copolymers wherein the copolymers are grafted (i.e., covalently bound) in the complex. There does not appear to be any prior art where a complex comprising a nucleic acid molecule and a charged copolymer of Formula I, wherein the charge copolymer is bound in the complex via ionic interactions (i.e. non-covalently bound).

The specification teaches that the following specific complexes were made and successfully used to deliver the nucleic acid molecule into cells: PEI/nucleic acid-P3YE5C (Example 9), Polylysine/nucleic acid-P3INF7 (Example 10), DOTAPcholesterol/nucleic acid-P3YE5C (Example 11), DOTAP/cholesterol/nucleic acid-P6YE5C (Example 12), and PEI/nucleic acid-P6YE5C (Example 12).

Since the art indicates that there are a number of obstacles which must be overcome in order to be able to predictably deliver a nucleic acid into a cell using polymers, additional experimentation would be required to fully enable the entire scope of the instant claims.

Considering the vast number of different compositions encompassed by the claims, an enormous amount of additional experimentation would be required. Furthermore, in addition to the obstacles recognized in the art, the fact that ionically bound copolymers have not been tested in the prior art, indicates that the additional experimentation required is not routine and it cannot be considered predictable that the entire scope of compositions encompassed by the claims would overcome all of the obstacles recognized in the art.

The level of the skill in the art is deemed to be high.

Considering the nature of the invention, the breadth of the claims, the unpredictable nature of the invention as recognized in the prior art, the limited amount of working examples and guidance provided, and the high degree of skill required to practice the invention, it is concluded that the specification does not provide an enabling disclosure for the full scope of the claims. Therefore, additional experimentation is required before one of skill in the art could make and use the claimed invention. The amount of additional experimentation required to perform the broadly claimed invention is undue.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-11, 13, 14, 16-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims explicitly encompass: homo- or hetero-bifunctional derivatives of an amphiphilic polymer (claim 1), amino acid derivatives (claim 1), peptide derivatives (claims 1, 4), spermidine derivatives (claims 1). However, the specification does not define these derivatives, nor are these derivatives considered art recognized terms such that one of skill in the art would recognize what each derivative is. As such, the instant claims are indefinite because the metes and bounds of the claim cannot be determined.

Response to Arguments

Applicant's arguments filed 11/27/2006, with respect to the rejection(s) of the claims under 35 USC 102 as being anticipated by WO98/19710 and 35 USC 103 as being obvious over WO98/19710 in view of U.S. Patent 5,863,984 have been fully considered and are persuasive. Therefore, the rejection(s) are withdrawn. However, upon further consideration, a new ground(s) of rejection is made under 35 U.S.C. 112, first and second paragraphs for the reasons indicated herein.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on 9:00 a.m.- 5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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